

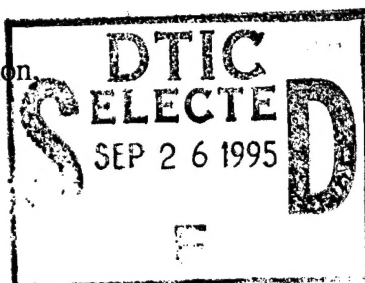
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September 18, 1995

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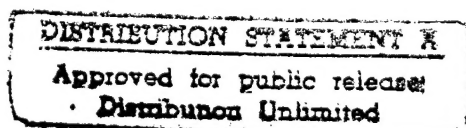
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Technical Report No. 18

DICHLOROBORANE-DIMETHYL SULFIDE, A HIGHLY SELECTIVE REDUCING AGENT FOR REDUCTION OF ORGANYL AZIDES TO AMINES

by

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<p>Dichloroborane-dimethyl sulfide reduces a variety of organyl azides, including primary, secondary, tertiary alkyl, cycloalkyl, aromatic and benzylic, to the corresponding amines in excellent yields. The reagent is highly selective and many functional groups, such as halogen, ester, nitrile, aliphatic and aromatic nitro, survive in this process.</p>					
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DICHLOROBORANE-DIMETHYL SULFIDE, A HIGHLY SELECTIVE REDUCING AGENT FOR REDUCTION OF ORGANYL AZIDES TO AMINES

Ashok M. Salunkhe¹ and Herbert C. Brown*

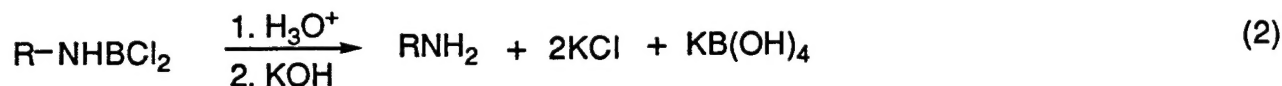
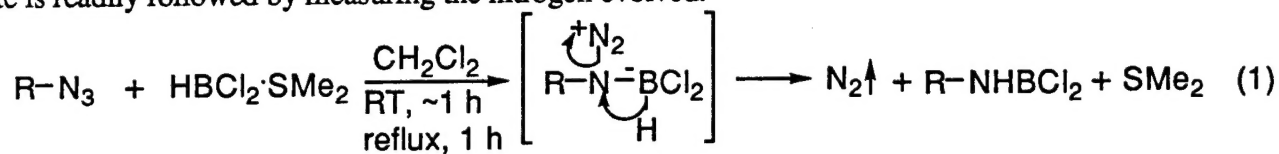
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Abstract: Dichloroborane-dimethyl sulfide reduces a variety of organyl azides, such as primary, secondary, tertiary, and aromatic to the corresponding amines in excellent yields. Cycloalkyl and benzylic azides are also readily reduced by this reagent. The reduction of azide with $\text{BHCl}_2\cdot\text{SMe}_2$ is highly selective and many functional groups, such as halogen, ester, nitrile, aliphatic and aromatic nitro, survive in this process.

The azido functionality is very useful in organic synthesis, especially for the introduction of amino groups by the reduction of azides.² Since many excellent methods are now available for the preparation of azides with excellent regio-, enantio- and stereocontrol, reduction of the azide group permits a controlled introduction of an amine function.³ The most commonly employed reagents for this purpose, lithium aluminum hydride⁴ and catalytic hydrogenation⁵ are relatively unselective, so there is considerable interest in the development of more selective methods. Sodium borohydride does not reduce azides satisfactorily at room temperature.^{6a,b} However, sodium borohydride in the presence of a phase transfer catalyst^{6c} and on an ion-exchange resin support^{6d} reduces aryl and arylsulfonyl azides to the corresponding products. On the other hand, sodium borohydride in the presence of nickel (II) chloride^{6e} works well for the reduction of both alkyl and aroyl azides. Recently, reduction of azides with $\text{Zn}(\text{BH}_4)_2$ has been reported in the literature.^{6f} Although this "reagent" is selective, and aroyl and acyl azides are readily reduced, the reduction of aliphatic and benzylic azides is slow and required 6-8 h of sonication in the presence of silica gel to get the corresponding amines in reasonably good yields. More importantly it has not been shown that this " $\text{Zn}(\text{BH}_4)_2$ "⁷ reduces tertiary alkyl azides to the corresponding amines. Several reagents^{6g} have been reported in the literature for the reduction of azides however little attention has been focused on the reduction of azides using boranes.⁸ Thus, lack of simple, general and highly selective reducing agent and our past experience in the area of selective reduction⁹ of various functionalities with boranes prompted us to initiate a systematic investigation of the reduction of organyl azides with boranes. In this communication we report preliminary results for the reduction of representative azides with commercially available $\text{BHCl}_2\cdot\text{SMe}_2$ in dichloromethane as a solvent.

1-Hexyl azide was chosen as a representative example for the initial study of the reduction of azides with boranes and the reactions were followed by measuring the nitrogen evolution. Among the various boranes, such as dialkyl, alkoxy, and haloboranes, studied for this purpose,¹⁰ $\text{BHCl}_2\cdot\text{SMe}_2$ emerged as the most suitable reagent of the ten reagents tested for the reduction of 1-hexyl azide to the corresponding amine. The reaction is mildly exothermic and 1-hexyl azide is reduced almost quantitatively to the corresponding amine. Having found a suitable reagent and established favorable reaction conditions for the reduction of 1-hexyl azide, we turned our

attention to testing the applicability of $\text{BHCl}_2\cdot\text{SMe}_2$ for the reduction of representative organyl azides. It was observed that this reagent reduces a variety of organyl azides of various structural requirements, including tertiary alkyl, aromatic, cyclic and benzylic azides, in a short period and in excellent yields (eqs 1 and 2). Moreover the rate is readily followed by measuring the nitrogen evolved.



The following procedure for the reduction of 2-azidoundecane is representative. A dry 25-mL flask equipped with a magnetic stirring bar, septum inlet and reflux condenser was charged with a one molar dichloromethane solution of $\text{BHCl}_2\cdot\text{SMe}_2$ (7.5 mmol). The reaction flask was connected to a gas buret through a Dry Ice-acetone trap to measure the evolved nitrogen. To this, 2-azidoundecane (5 mmol, 0.985 gms) was added slowly at room temperature and the reaction was monitored by the nitrogen evolved in the reduction (no hydrogen is evolved). The addition of the azide is completed in 35-40 minutes. In this time the reaction is ~75% complete as indicated by the nitrogen evolved. The reaction mixture was then refluxed for one hour in order to achieve a complete reduction in a reasonably short period of time. Solvent was removed from the reaction mixture under vacuum and the intermediate was hydrolyzed with conc. hydrochloric acid by heating at 80 °C for 35-40 minutes. It was then cooled to room temperature and made strongly alkaline with aqueous potassium hydroxide. The reaction mixture was extracted with ethyl ether (3 x 15 ml) and the combined ethyl ether extracts were washed with water, brine, and dried over anhydrous magnesium sulfate. Removal of the solvent gave the 2-undecylamine in 85 % isolated yield. The results are summarized in Table 1.

Table 1. Reduction of Representative Azides with $\text{BHCl}_2\cdot\text{SMe}_2$ in Dichloromethane^a

Entry	Azide ^b	Amine ^c	Yield of Amine%
1	1-Azidohexane	Hexylamine	95 ^d
2	1-Azidododecane	Dodecylamine	78 ^e
3	2-Azidoundecane	2-Undecylamine	85 ^e
4	Azidocyclohexane	Cyclohexylamine	93 ^d
5	Azidocycloheptane	Cycloheptylamine	80 ^e
6	Phenyl azide	Aniline	94 ^d
7	Benzyl azide	Benzylamine	82 ^e
8	1-Azidoadamantane	Adamantanamine	75 ^e

^aAll reactions were carried out using 1.5 equivalents of $\text{BHCl}_2\cdot\text{SMe}_2$ in dichloromethane at 1.0 M concentration with respect to $\text{BHCl}_2\cdot\text{SMe}_2$. ^bOne equivalent of azide was used. ^cAll compounds gave satisfactory spectral analysis. ^d% Yield of the amine was calculated by ¹H NMR by adding internal standard. ^e% Yield of the isolated product.

All azides examined were reduced in a relatively short period of time and excellent yields of the corresponding amines were realized. This reagent has certain advantages over the currently available methods such as 1) it reduces aliphatic and benzylic azides to the corresponding amines in high yields and in relatively short period of time. 2) it also works for the reduction of tertiary alkyl and aryl azides. 3) the reductions were carried out in nonaqueous medium using dichloromethane as a solvent, this avoids the problems associated with methanol^{6c} or water,^{6d} for easily hydrolyzable functionalities. 4) the reaction is simple and the rate is readily followed.

Our earlier study of the reaction of chloroboranes with representative organic compounds had revealed that dichloroborane is a very mild reducing agent.¹¹ This reagent in THF at 0 °C works exceptionally well for the deoxygenation of sulfoxides to sulfides,¹¹ but does not reduce esters, nitriles, nitro compounds, etc. Aldehydes, ketones and amides are reduced only slowly, whereas other functional groups, such as amine oxides, are either inert or reduced very slowly. These findings suggested the possibility of achieving a highly selective reduction of the azido group with $\text{BHCl}_2\cdot\text{SMe}_2$ in the presence of other readily reducible functional groups.

In order to explore the selectivity of this reaction, the reduction of 1-hexyl azide was studied with $\text{BHCl}_2\cdot\text{SMe}_2$ in the presence of an equivalent amount of ethyl benzoate, 1-bromohexane, benzonitrile, nitropropane, and nitrobenzene. The azide was selectively reduced and the added reducible compound was recovered in essentially quantitative yield. The results are summarized in Table 2.

Table 2. Selective Reduction of 1-Hexyl Azide with $\text{BHCl}_2\cdot\text{SMe}_2$ in Dichloromethane at Room Temperature in the Presence of Other Reducible Compounds^a

Entry	Reducible Compound ^b	% of Amine ^c	Recovery of the ^d Reducible Compound %
1	1-Bromohexane	74	94
2	1-Nitropropane	75	100
3	Nitrobenzene	76	100
4	Benzonitrile	72	93
5	Ethyl Benzoate	75	97

^aAll reactions were carried out at room temperature in dichloromethane at 1.0 M concentration with respect to reducible compound and 1-hexyl azide. ^bOne equivalent of reducible compound and one equivalent of $\text{BHCl}_2\cdot\text{SMe}_2$ was used. ^cAmine (%) by nitrogen evolution in 1.0-1.5 h. ^dRecovery of reducible compounds calculated by ¹H NMR (300 MHz) by adding suitable internal standard.

Since $\text{BHCl}_2\cdot\text{SMe}_2$ is a poor hydroborating reagent,¹² the presence of double bonds (C=C) in the azide should not be affected by the reagent. Preliminary experiments have confirmed this.

In conclusion, we have demonstrated the successful utilization of $\text{BHCl}_2\cdot\text{SMe}_2$ as a new highly selective reducing reagent for achieving the reduction of organyl azides in good yields. The reduction of the azido group with $\text{BHCl}_2\cdot\text{SMe}_2$ has many advantages over currently available methods because of an exceptional selectivity for the azido group. Azides are selectively reduced in the presence of halides, nitriles, esters, alcohols, and amides.

nitro groups. The reagent also reduces in excellent yields representative organyl azides of variable structural requirements including secondary, tertiary, cyclic, aromatic and benzylic azides.

Acknowledgment:

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